REMARKS

A listing of the Claims is provided for the Examiner's convenience. However, no amendments are made to the claims. The following addresses the substance of the Office Action.

Obviousness

Claims 1-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hashmi et al. (WO 01/07079), Tamura et al. (1975 *Immunology* 28:909-924) and Folds et al. (1983 *J Clin Microbiol* 18:321-326). Hashmi et al. relates to a vaccine formulation that provides for the extended release of antigenic material over time. The Examiner acknowledged that this reference fails to teach progressively increasing doses of the antigenic material over time. The Examiner relied on Tamura et al. and Folds et al. to support the conclusion that it would have been *prima facie* obvious to modify the teachings of Hashmi et al. by the teachings of Tamura et al. and Folds et al. and arrive at the presently claimed methods. However, as discussed below, there are no teachings in any of the cited references with regard to progressively increasing doses of one or more biologically active agents. For this reason, the combination of cited references fails to establish a *prima facie* showing of obviousness.

Tamura looked at the influence of pre-exposing mice to carrier alone in advance of injecting hapten-conjugated carrier. In particular, Tamura et al. presensitized mice with carrier, i.e., sheep red blood cells (SRBCs), and then injected the mice with hapten (TNP)-conjugated SRBCs. They looked at the ability of mice to develop anti-hapten antibodies as a function of the amount of carrier antigen given at presensitization. In the second full paragraph on page 921, Tamura et al. showed that prior priming with a relatively low carrier antigen dose (i.e., a low dose of SRBCs) brought about an enhanced anti-hapten antibody response (Fig. 3)." Referring to Figure 3, it is evident that the highest anti-TNP antibody titer was achieved with a relatively low presensitization dosage of SRBC (i.e., 2×10^6) as compared to a relatively high dosage of TNP-SRBC (i.e., 2×10^8).

The Examiner noted the abstract of Tamura et al., which states at the second paragraph: "When mice were presensitized with i.p. injections of SRBC and boosted with i.p. injections of TNP-SRBC, the anti-TNP antibody production was maximally enhanced by presensitization with a low dose of SRBC, and gradually abolished with higher doses of SRBC for presensitization". However, the point of the study by Tamura et al. was to examine the effect of presensitizing with various amounts of a carrier antigen alone in advance of injection with hapten conjugated carrier.

The study did not administer progressively increasing doses of the biologically active agent of interest (i.e., TNP conjugated to SRBC carrier).

Thus, Tamura does not teach administration of progressively increasing doses of biologically active agent as covered by the present claims. By way of contrast, Tamura only investigated what effects various doses of carrier alone have on antibody production when an animal is subsequently exposed to hapten-conjugated carrier. The reference does not investigate what effect progressively increasing doses of one or more biologically active agents have on an individual animal over a period of time. For example, on page 913 the reference states:

> The maximum enhancement of anti-TNP production was observed in mice presensitized with 2 x 10^6 SRBC and the increase in dose of SRBC for pre-sensitization brought about the decrease of such an enhancement. On the other hand, anti-SRBC antibody responses were heightened with increase in dose of carrier SRBC. Fig.3b shows that on day 6 after injection of 2 x 10^8 TNP-SRBC in non-pretreated mice, considerable amounts of both MES (IgM) and MER (IgG) anti-hapten antibodies were observed.

The fact Tamura did not investigate progressively increasing doses is indeed not surprising when one considers that Tamura is solely concerned with understanding the effect of intraperitoneal or subcutaneous injection of carrier alone on subsequent anti-hapten antibody and hypersensitivity responses following injection of hapten-conjugated carrier.

Similarly, Folds et al. also fails to teach the progressively increasing doses of the present application's claims. The Examiner stated that Folds et al. teaches *Rickettsia ricketsii* vaccine models, which show greater protection when higher doses of vaccine were given and when frequent booster injections were administered. However, Folds et al. is not concerned with the beneficial effects of the presently claimed processes, which require progressively increasing doses. In contrast, Folds et al. examined the effects of an initial dose of either 0.5 ml of a 1:3 dilution or 0.5 ml of a 1:100 dilution of vaccine in separate sets of guinea pigs, followed by booster injections, which were not an increased dose. For example, page 322, left column under the header "Determination of optimal dose of vaccine and requirements for booster vaccination," and at Table 5 on page 324, Folds et al. states that booster vaccinations of the same dose were given on day 30 after the first inoculation.

In view of the foregoing, it is therefore clear that none of the cited references teach progressively increasing doses being administered to a subject as claimed in Claims 1-9. Accordingly, one of ordinary skill in the art would have had no reason to develop the presently

claimed processes based on the cited references. As such, the Applicant respectfully requests the rejection be withdrawn.

Claims 10 and 31 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Hashmi et al., Tamura et al. and Folds et al. (as discussed *supra*) in further view of Sako et al. (WO 94/06414). Sako et al. teaches a hydrogel-type sustained release preparation comprising a drug. However, Sako et al. does not provide any information about administering progressively increasing doses to a subject. Thus, Sako et al. fails to fill the gap between the presently claimed processes and the disclosures of Hashmi et al., Tamura et al. and Folds et al. as discussed above. As such, the rejection of Claims 10 and 31 should also be withdrawn.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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